REMARKS

Claims 1-70 are pending. Claims 1-11 and 13-64 are withdrawn from consideration, and claims 65-70 are canceled. Claims 72-76 are amended.

Support for the Amendments

The amendments are substantially to correct inadvertent typographical errors in claim dependency. No new matter has been added.

The amendments to the claims should in no way be construed as acquiescence to any of the Examiner's rejections and were made solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Withdrawal of Objection to the Specification

Applicant thanks the Examiner for withdrawal of the objections to the specification.

Withdrawal of Rejections under 35 U.S.C. §112, Second Paragraph

Applicant thanks the Examiner for withdrawal of the rejection of claim 12 under 35 U.S.C. §112, second paragraph for indefiniteness.

Withdrawal of Rejections Under 35 U.S.C. §102

Applicant thanks the Examiner for acknowledging the priority document, perfection of the priority claim in the instant case, and withdrawal of the rejections for anticipation

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Withdrawal of Rejections of Claim 12 Under 35 U.S.C. §103

Applicants thank the Examiner for the withdrawal of the rejection of claims for obviousness.

Rejections under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 73 and 75 under 35 U.S.C. §112, ¶2 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The term "said cancer cells" in line 5 of claim 73 is stated to lack sufficient antecedent basis for the limitation. Applicant thanks the Examiner for the careful reading of the claim. Line 3 of the claim has been amended as set forth above to recite "culturing cancer cells" to provide proper antecedent basis for "said cancer cells" in line 5. Withdrawal of the rejection is respectfully requested.

Claim 75 is rejected for not further limiting the subject matter of the claim from which it depends. Claim 75 is now dependent on claim 73 which recites "cancer cells." The dependent claim further limits the subject matter by reciting "human cancer cells." Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §112, First Paragraph

New Matter

The Examiner has rejected claims 12, 71, 72, 74, and 76 under 35 U.S.C. §112, ¶1 as failing to comply with the written description requirement for containing new matter. The Examiner asserts that the specification does not provide support for culturing cells in the presence of the test substance for "at least three months." Applicant respectfully disagrees.

The Examiner has pointed to page 69, lines 11-14 of the specification to support the assertion for a lack of support. However, it is the next sentence that provides support for the limitation of "at least three months." Applicants have reproduced the portion of the specification below with the subsequent sentence:

> When a known antiandrogen drug (for example, bicalutamide, flutamide, and the like) is used in the production method of the present invention for a mutant AR-expressing cancer cell line, an antiandrogen drug-resistant line expressing a mutant AR can be established at latest in about 3 months or so. *However, depending on the kind of compound, we can expect a case wherein cell proliferation is not induced even when cultivation is continued for a longer period.* [emphasis added]

Applicant submits that in reading the sentences together, that one would understand "a longer period" to mean "a longer period than three months" providing support for the claim limitation "at least three months."

Moreover, Example 1 (page 78, lines 6-10) teaches that initiation of proliferation may take up to 13 weeks.

> When LNCaP-FGC (ATCC Number: CRL-1740) is cultured in a culture broth (RPMI1640+10% Dextran Charcoal (DCC)-Fetal Bovine Serum (FBS)) containing 0.1 and 1 μM bicalutamide (commercial name: Casodex), it does not proliferate initially. However, when cultivation was continued for 6 weeks to 13 weeks or more, two cell lines exhibiting proliferation were obtained.

Applicant submits that culturing of cells for 13 weeks provides support for the term "at least three months."

Applicant notes that the test for support is not an *in haec verba* requirement. Newly added claim limitations must be simply supported in the specification through express, implicit, or inherent disclosure. Applicant submits that "at least three months" is supported by the specification. Withdrawal of the rejection is respectfully requested.

Biological Deposit Required

The Examiner has rejected claim 73 under 35 U.S.C. §112, ¶1 as failing to comply with the enablement requirement because the specification does not provide evidence that the claimed biological materials are (a) known and readily available to the public; and (b) reproducible from the written description. Applicant respectfully disagree.

The Examiner asserts that it is unclear that a cancer cell line which comprises a leucine or a cysteine for a tryptophan at amino acid number 746 of SEQ ID NO: 2 is known or publicly available, or can be reproducibly isolated without undue experimentation. The Examiner further states that it is not clear if the Applicant intend that the mutated AR should be subcloned into an expression vector and transfected into a host cell for use in the assay system.

Applicant submits that the specification, provided with the knowledge of those of ordinary skill in the art, provides ample teachings regarding methods to generate cell lines that fall within the scope of the claims, and that the specific method of making the cell lines for use in the claimed method of the invention is not a limitation of the invention.

First, a cancer cell line expressing the mutant AR defined in claim 73 can be reproducibly obtained based on the method disclosed in Example 1 without undue

experimentation. The present invention includes the finding that AR mutations are generated at specific "hot spots" based on treatment with various antiandrogen agents and can be reproduced *in vitro*. On page 67, lines 7-15, the specification states:

> *The mutation site of the mutant AR obtained as described above is characteristic depending on the kind of antiandrogen drug used as the selection pressure*; for example, when bicalutamide is used, mutations frequently occur in tryptophan at amino acid number 746 in the amino acid sequence represented by SEQ ID NO: 2 (it is preferably substituted by leucine or cysteine); when flutamide is used, mutations frequently occur in threonine at amino acid number 882 in the amino acid sequence represented by SEQ ID NO: 2 (it is preferably substituted by alanine). These mutation sites agree well with mutation sites that have been clinically found from relapsed cancers to endocrine therapies using respective antiandrogen drugs. [emphasis added]

To obtain a cell line containing an AR with two mutations, as in claim 74, one could use a commercially available cell line such as LNCaP-FGC (ATCC No. CRL-1740), which contains a mutation in SEQ ID NO: 2 at amino acid threonine 882 (see page 74, lines 3-4), can be treated with bicalutamide. Applicant submits that obtaining commercially available cancer cells described in the specification and growing cells in culture in the presence of antiandrogen agents, although potentially time consuming, is routine in the art. No deposit of biological material is required.

Moreover, many methods are known in the art for making cell lines with genes including point mutations. Such methods are included in the specification. For example, one source of cells for use in the method of the invention is transgenic animals (see, e.g., page 64, line 26ff). Applicant submits that methods of making transgenic animals is routine in the art, and using tissues from such animals to create cancer cell lines or immortal cell lines is also routine.

Applicant enclose herewith a review by Erikson entitled "Creating Animal Models of Genetic Disease," published in *American Human Genetics* in 1988, fourteen years before the priority date of the instant application (2002). The text teaches a number of mice that were generated to include mutations in various genes, demonstrating the method was routine in the art at the time of the publication of the review. Figure 1 is a flowchart showing the method of

making transgenic mice. The transfection and screening methods for embryonic stem cells can be readily used with cancer cell lines to obtain cell lines with the desired AR sequences.

Alternatively, methods for generation of recombinant cells are provided, for example, in U.S. Patent 6,306,605 entitled "Methods for Making Recombinant Cells" having a priority date of December 3, 1998 and issued on October 23, 2001 (copy enclosed). Many other methods were also routine in the art at the time of filing of the priority document of instant application.

In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) sets forth the test for factors to be considered in determining if undue experimentation is required. Applicants submit that the Examiner is not considering what is an ordinary amount of experimentation in the art of the instant application and what is a predictable event. This must be considered in the analysis of what constitutes "undue experimentation." *In re Wands* states:

> The determination of what constitutes undue experimentation in a given case requires application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* (citation omitted). The test is not merely quantitative because a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. (pg. 1404)

Applicants submit that the experimentation required to generate cell lines useful in the methods of the invention is routine, and the specification provides substantial guidance with respect to the direction in which experimentation should proceed.

The invention of the instant application includes the finding that specific antiandrogen agents produce characteristic changes at "hot spots" in the androgen receptor. Culture methods for cells in bicalutamide are provided in Example 1. Selection of a different antiandrogen agent for culture of cells is a trivial change. Maintenance of cells in culture is routine. Selection and generation of expression vectors containing desired wild-type or mutated sequences is within the ability of those of skill in the art. Identification of cells or animals expressing the desired gene is within the ability of those of skill in the art.

The level of skill in the art of biomedical research is high. Applicants submit that those skilled in the art frequently have at least doctoral level training. Therefore, despite the fact that technical skills are required to perform routine experiments, the skills are in the possession of those of skill in the art.

The Examiner seems to suggest that in order for the claim to be enabled, it is necessary for each attempt to generate a cell line that for use in the claimed methods be successful. Applicants respectfully disagree. *In re Wands* teaches that a limited level of success, so long as there is some success, is sufficient to meet the enablement requirement.

During prosecution Wands submitted a declaration under 37 C.F.R. §1.132 providing information about all of the hybridomas that Appellants had produced before filing the patent application. The first four fusions were unsuccessful and produced no hybridomas. The next six fusion experiments all produced hybridomas.

Of all of the fusion experiments performed by Wands, only four of the nine fully characterized hybridomas produced antibodies that fell within the scope of the claims. Wands did not teach an improved method for making hybridomas. Wands taught and claimed a method that required the use of hybridomas having specific claimed characteristics. An additional 134 hybridoma lines were frozen and stored without further analysis. The number of these hybridomas that produce antibodies that fall within the limitations of the claims is unknown.

In re Wands demonstrates that routine experimentation is not always trivial or successful. Routine experimentation can include animal testing. Routine experimentation, by the nature of it being experimentation, has some aspect of uncertainty in regard to result, which is tolerable within the scope of enablement. If the experimental path and data analysis have sufficient certainty (i.e., are routine), the claims are enabled. *In re Wands* makes it clear that not all outcomes from routine experimentation need to fall within the scope of the claims in order for the claims to be enabled.

Applicant submits that the method of making cell lines required to practice the method of the invention is at least as routine as the method to make hybridoma cells expressing the desired antibody at the time of filing of the Wands application. The claims are fully enabled and no deposit of biological material is required. Withdrawal of the rejection is respectfully requested.

SUMMARY

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicants believe that no fee is due to consider the present amendment. Nevertheless, the Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105 referencing Docket No. 68138(46590).

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Respectfully submitted,

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